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Chondrosarcoma in a Patient with McCune-Albright Syndrome.

*Report of a Case**

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ABSTRACT

A case of McCune-Albright syndrome with acromegaly and chrondrosarcoma is reported. The potential role of chronic growth hormone overproduction in the occurrence of malignant transformation and the possible value of bisphosphonates in the treatment of bone fibrous dysplasias are discussed.

McCune in 1936 [1] and Albright in 1937 [2] described the first cases of polyostotic fibrous dysplasia accompanied with cutaneous pigmentation and precocious sexual development. Sarcomas can arise in McCune Albright syndrome and other fibrous dysplasias. Osteosarcoma is the most common histologic type, whereas few cases of chondrosarcoma have been reported. We report the case of a chondrosarcoma in a patient with polyostotic fibrous dysplasia and acromegaly but no skin lesions. To our knowledge, a single similar case has been reported [3].

Case-report

A 27-year-old woman was admitted in 1990 for headache, diplopia, and vomiting. Her physical appearance was strongly suggestive of gigantism, with a height of 205 cm, a weight of 110 kg, broad hands and feet, and prognathism. She had had a normal puberty but reported amenorrhea since the age of 21. A visual field study showed bitemporal hemianopsia. Funduscopy findings were normal. Growth hormone and insulin-like growth factor 1 were elevated (124 ng/ml [normal, 0.5-1.5] and 90 IU/ml [normal, 0.58-2 IU/ml] respectively), as was serum prolactin (53 [normal, ≤ 30]). A large mass occupying and extending above the sella turcica was demonstrated by computed tomography and magnetic resonance imaging of the brain. Surgery via the transsphenoidal approach allowed to remove only part of the tumor. Radiation therapy was given. Histology showed a pituitary adenoma with a positive immunological stain for growth hormone only. Growth hormone and insulin-like growth factor levels were still elevated (5.1 ng/ml and 4.5 IU/ml, respectively) several weeks after the end of radiation therapy. Bromocriptine (15 mg/day) was given, to no effect. Octreotide (300 µg/day) was then prescribed but had to be stopped promptly because of gastrointestinal side effects.

In 1991, she was admitted to a rheumatology department for mechanical pain in her right thigh exacerbated by palpation of the thigh muscles. There were no other rheumatic symptoms. Peripheral blood cell counts were normal. Abnormalities in calcium and phosphate levels were found in blood and urine (Table I). Plain radiographs demonstrated evidence of polyostotic fibrous dysplasia involving the femurs (fig. 1), tibias, feet, right humerus, and right ulna. The affected bones were hyperactive on a radionuclide bone scan.

Magnetic resonance imaging of the left thigh (fig. 2) disclosed a large mass arising from the femur and extending to the adjacent muscles. A surgical biopsy established a diagnosis of grade II chondrosarcoma but was followed by a fracture of the femur. Amputation with disarticulation of the hip was performed. Three months later, the patient reported persistent pain in her right femur. There was no evidence of a metastasis, and the pain was ascribed to the fibrous dysplasia. Pamidronate was started, in a dose of 60 mg/day for three consecutive days every six months. The pain abated, and improvements were seen in calcium and phosphate levels and in bone mineral content measured by absorptiometry at a

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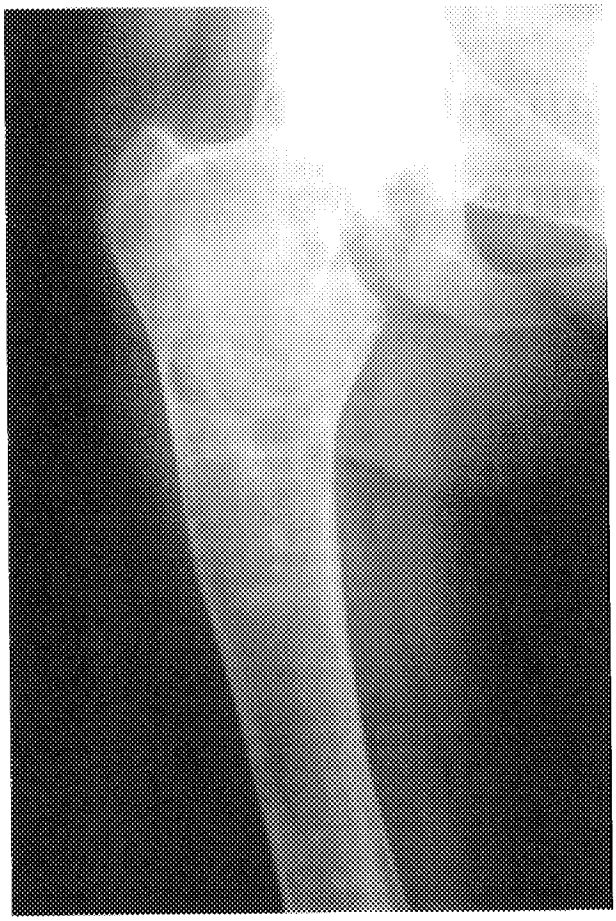

Fig. 1. - Plain radiograph of the right femur demonstrating typical osseous dysplasia.

focus of fibrous dysplasia in the iliopubic ramus and at a nondysplastic site of the spine. The time-course of these parameters over a three-year period are summarized in Table I.

A mass arising from the right tibia was found in 1995 and demonstrated by histology to be a grade II chondrosarcoma. Above-the-knee amputation was performed. A similar tumor developed one year later at the neck of the right femur, requiring amputation with disarticulation of the hip. Whether this tumor was a metastasis of the previous chondrosarcoma or a new primary remains unclear since genetic studies were not done. The patient died a few months later with multiple metastases.

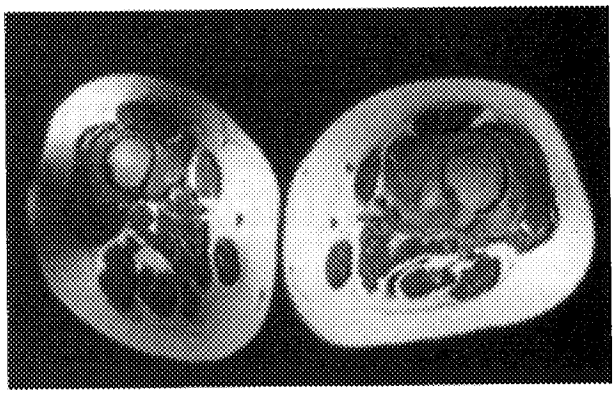

Fig. 2. - Magnetic resonance imaging of the left thigh showing a mass arising from the femur and extending to the adjacent muscles.

Discussion

Polyostotic fibrous dysplasia, cutaneous pigmentation, and precocious sexual development is the classic triad defining McCune Albright syndrome. Although sexual precocity is the most common endocrine abnormality, acromegaly [4,5] and other endocrinopathies have also been reported. It has been suggested [7] that McCune Albright syndrome should be defined as presence of an endocrinopathy with either cutaneous pigmentation or polyostotic fibrous dysplasia. Our patient met this definition. However, we did not perform molecular studies to look for a mutation in the GNAS1 gene encoding the α subunit of the protein G responsible for adenylate cyclase activation.

The incidence of malignant transformation of bone lesions has been estimated at 0.5% in polyostotic

TABLE I. - Calcium and phosphate levels in serum and urine and bone mineral content measured by absorptiometry before and after intravenous pamidronate therapy.

	Before pamidronate	After 6 months	After 1 year	After 2 years
Serum calcium (2.10 -2.65 mmol/l)	2.43	2.46	2.38	2.4
Serum phosphate (0.80-1.45 mmol/l)	0.84	0.91	0.91	1.01
1.25 OH vit D (12-32 pg/ml)	34	26	33	28
Parathyroid hormone (10-60 pg/ml)	22	17	27	20
Osteocalcin (3.7-6.9 ng/ml)	132	64	57	55
Urinary calcium (1.5-6.25 mmol/24H)	19	9.73	7.6	8.4
Urinary phosphate (22-42 mmol/24H))	73	29.3	36	27
Urinary hydroxyproline (100-350)	1700	566	651	422
Bone mineral density (g/cm^2) : (hip + spine)	1.025	1.068	1.12	1.183

fibrous dysplasia and 4% in McCune Albright syndrome. Females and males are equally affected. Radiation therapy to the bones may increase the risk of sarcomatous transfomation. Osteosarcoma accounts for 60% of cases [8]. Chondrosarcoma has been reported in 11 patients with isolated fibrous dysplasia and a single patient with McCune Albright syndrome [3]. The tumors arose most often in the skull and face, followed by the femur and tibia. Pain was the most suggestive symptom. Two of 11 (19%) McCune Albright patients with malignant transformation had acromegaly [9,10]. Evidence from animals and humans is consistent with a link between somatotropic activity and tumorigenesis. Patients with acromegaly are at high risk for benign and malignant colonic tumors, meningiomas, and mesenchymatous tumors [11]. Thus, our case and cases from the literature suggest that acromegaly may be a risk factor for malignant transformation in McCune Albright syndrome.

Fibrous dysplasia is characterized by a high bone turnover rate. Neither calcitonin nor etidronate have been found effective. Beneficial effects of intravenous pamidronate in patients with polyostotic fibrous dysplasia have been reported recently [12]. In our patient, intravenous pamidronate alleviated functional symptoms and improved calcium and phosphate levels, as well as absorptiometry measurements, over a three-year period.

In conclusion, our case suggests that chronic growth hormone overproduction may increase the risk of sarcomatous transformation in McCune Albright patients with acromegaly. It also indicates that intravenous pamidronate may improve the fibrous dysplasia lesions characteristic of McCune Albright syndrome.

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